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THÈSE

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DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en Radiologie et Imagerie Médicale

Vessel's bifurcation geometry remodelling in de-novo and growing intracranial aneurysms. A multicentre study.

MODIFICATIONS DE LA GEOMETRIE VASCULAIRE DES BIFURCATIONS INTRACRANIENNES PORTEUSES D'ANEVRYSMES DE NOVO OU EN CROISSANCE. ETUDE MULTICENTRIQUE.

BOUCHERIT Julien

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Sous la direction de Monsieur le Docteur L'ALLINEC Vincent

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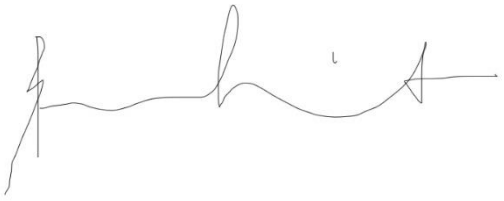

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Au présent, que j'échange trop souvent contre une promesse.

Aux patients.

Liste des abréviations

3D	Three-Dimensional
ACA	Anterior Cerebral Artery
ADPKD	Autosomal Dominant Polycystic Kidney Disease
aOR	adjusted Odd-Ratio
CI	Confidence Interval
CT(A)	Computed Tomography (Angiography)
DA	Daughter Artery
DSA	Digital Subtraction Angiography
eNOS	endothelial Nitric Oxide Synthase
IA	Intracranial Aneurysm
INSERM	Institut National de la Santé Et de la Recherche Médicale
IQR	Interquartile Ranges
JENI-RC	Jeunes en Neuroradiologie Interventionnelle-Research Network
MCA	Middle Cerebral Artery
MIP	Maximum Intensity Projection
MRI	Magnetic Resonance Imaging
NO	Nitric Oxide
PA	Parent artery
SD	Standard Deviation
UMR	Unité Mixte de Recherche
WSS	Wall Shear Stress

CONTEXTE

L'anévrysme intracrânien est une malformation vasculaire artérielle. Il s'agit d'une dilatation focale qui se présente le plus souvent de façon sacculaire, c'est-à-dire sous la forme d'une hernie de taille variable implantée sur la paroi artérielle par l'intermédiaire d'un collet.

C'est une pathologie fréquente qui concerne environ 3% de la population générale, et qui survient indépendamment de la répartition géographique et de l'ethnie (1). Elle se développe le plus souvent entre 35 et 60 ans, et est plus fréquente chez la femme.

Sa principale complication est la rupture, et l'hémorragie sous-arachnoïdienne qui en résulte présente encore à l'heure actuelle un pronostic sombre, même s'il a été amélioré ces dernières décennies. Les chiffres sont variables selon les études mais on peut retenir que 20 % environ des patients décèdent avant d'arriver à l'hôpital (2), et que parmi les patients vivants pris en charge à l'hôpital 30 % des patients décèderont, majoritairement dans la première semaine qui suit l'hospitalisation du fait d'un resaignement, d'un vasospasme, ou d'une hydrocéphalie. Parmi les patients qui survivent, environ 1/3 présenteront des séquelles neurologiques invalidantes, 1/3 un handicap léger souvent d'ordre cognitif, et seulement 1/3 des patients retrouveront une vie normale soit moins de 20% de l'ensemble des patients (3).

Dans la majorité des cas, il s'agit d'une pathologie acquise, c'est-à-dire qu'elle apparait lors du développement de l'individu. Certains facteurs de risque prédisposant à la formation des anévrysmes intracrâniens sont bien identifiés, et on pourra citer tout particulièrement le tabagisme et l'hypertension artérielle (4–6).

Il existe cependant une héritabilité de cette pathologie et le rôle de facteurs génétiques dans la pathogenèse a été suggéré par un certain nombre de travaux (7,8). Il existerait d'une part des formes familiales, même si le schéma héréditaire n'est pas bien élucidé (9), et que la part environnementale et épigénétique est vraisemblablement largement sous-estimée (10).

D'autre part certaines pathologies héréditaires plus rares sont également connues pour être associées à un risque significativement accru de survenue et de rupture d'un anévrysme

intracrânien, parmi lesquelles la polykystose rénale dans sa forme autosomique dominante, le syndrome d'Ehlers-Danlos, ou encore les dysplasies fibromusculaires.

Les anévrysmes intracrâniens siègent le plus souvent sur les bifurcations artérielles du polygone de Willis et sont multiples dans environ 20 % à 30 % des cas (3) (Figures 1 et 2).

L'étiopathogénie de l'anévrysme intracrânien est imparfaitement élucidée, de même que les facteurs influençant la naissance ou la rupture anévrismale. De ce fait de nombreuses voies de recherches existent parmi lesquelles on peut citer la génétique, l'étude du transcriptome, ou encore l'imagerie de la paroi anévrysmale (8,11,12).

Il est communément admis que ceux-ci se formeraient et évolueraient progressivement au niveau de zones de moindre résistance de la paroi artérielle, sous l'effet de variations hémodynamiques.

Le fait qu'ils surviennent dans des sites préférentiels bien identifiés s'expliquerait notamment par la configuration locale qui favoriserait les effets de flux sur la paroi et le remodelage de celle-ci. En particulier au niveau des bifurcations, la distribution du flux sanguin génère une augmentation des contraintes de cisaillement de la paroi (Wall Shear Stress) dans la zone de séparation des artères filles (13), conduisant d'une part à une augmentation du renouvellement cellulaire dans la paroi vasculaire, et d'autre part à une diminution des niveaux d'oxyde nitrique synthase endothéliale (eNOS) qui, dans des circonstances normales, réduit l'inflammation et stabilise la structure de la paroi (14). En conséquence, ces altérations mèneraient à un remodelage inflammatoire de la paroi vasculaire, qui pourrait entraîner une modification des paramètres géométriques locaux.

Pourtant, la pathologie anévrysmale intracrânienne ne touche pas l'ensemble de la population ou bien même l'ensemble des bifurcations. En plus des facteurs de risque et des prédispositions familiales déjà évoqués, il existerait certains paramètres anatomiques qui influenceraient la formation de l'anévrysme intracrânien : par exemple l'angle de bifurcation serait plus large sur

les bifurcations porteuses d'anévrysmes, et les diamètres de l'artère porteuse ou des deux artères filles influenceraient le flux en regard de la bifurcation (15–21).

Le constat d'une anatomie prédisposante est généralement réalisé à partir d'imageries diagnostiques sur lesquelles l'anévrysme existe déjà. Il est alors difficile de savoir si l'anatomie décrite par ces études est la cause ou la conséquence de la présence de l'anévrysme ; en d'autres termes, ces paramètres géométriques pré-existent-ils à l'apparition d'un anévrysme ou est-ce la présence de celui-ci qui modifie localement la bifurcation.

C'est finalement l'éternelle question de « l'œuf ou de la poule » à laquelle nous avons essayé de répondre dans ce travail.

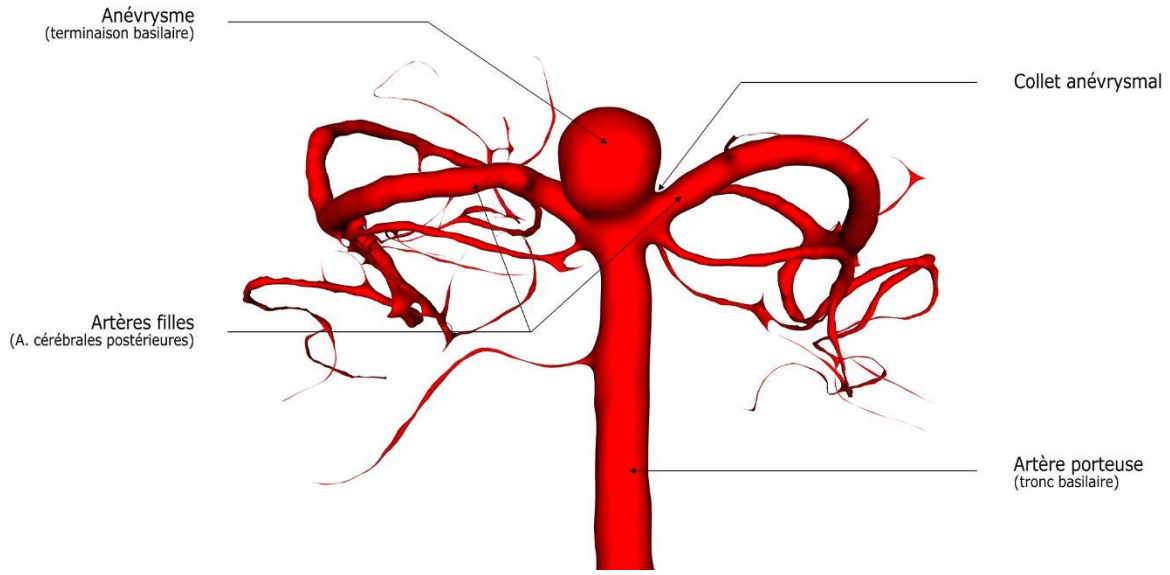

Figure 1. Anévrysme intracrânien

3D Volume Rendering partially cropped from DSA imaging

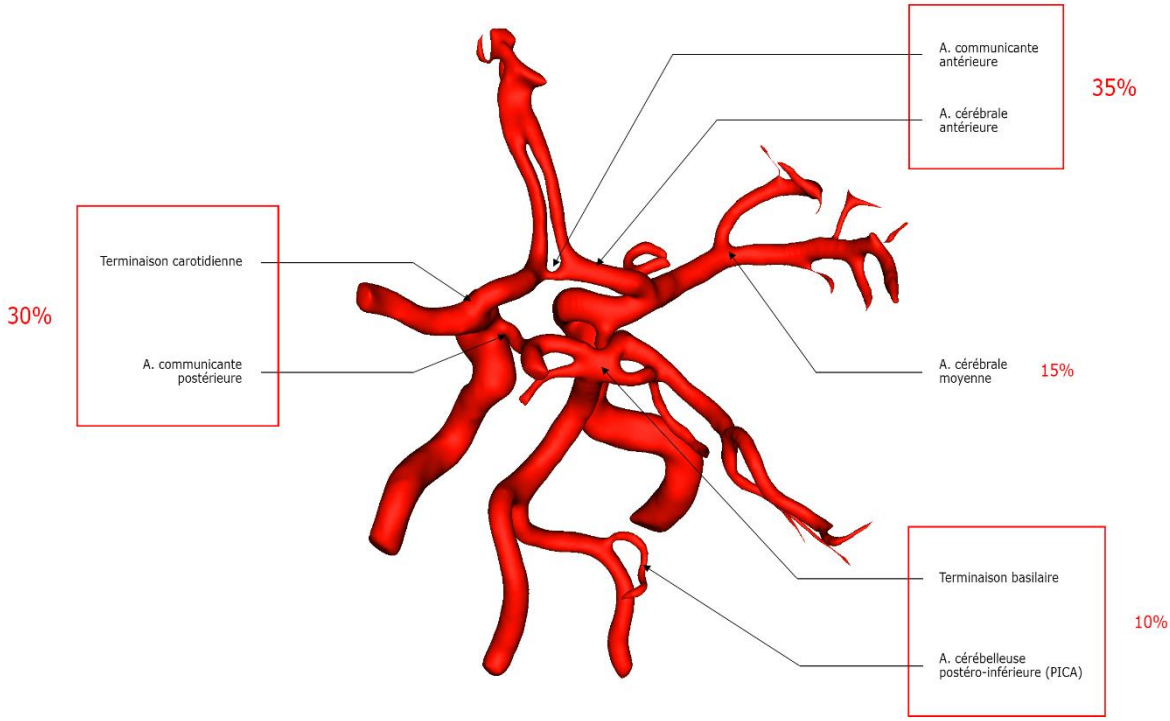

Figure 2. Polygone de Willis : topographie de la pathologie anévrysmale

3D Volume Rendering partially cropped from TOF imaging

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Plan

VESSEL'S BIFURCATION GEOMETRY REMODELLING IN DE-NOVO AND GROWING INTRACRANIAL ANEURYSMS. A MULTICENTRE STUDY.

BOUCHERIT Julien[1]; KERLEROUX Basile[2], MD, MSc; BOULOUIS Grégoire[3], MD, PhD; TESSIER Guillaume[4]; RODRIGUEZ-REGENT Christine[2], MD; SPORNS Peter[5,6], MD, MHBA, FESO; GHANNOUCHI Haroun[7], MD; SHOTAR Eimad[7], MD; GARIEL Florent[8], MD-MSc; MARNAT Gaultier[8], MD; BUREL Julien[9]; IFERGAN Héloïse[3], MD; FORESTIER Geraud[10]; ROUCHAUD Aymeric[10], MD, PhD; DESAL Hubert[4,13], MD, PhD; NOURI Anass[11], PhD; AUTRUSSEAU Florent[12], PhD; LOIRAND Gervaise[13], PhD; BOURCIER Romain[4,13], MD, PhD; L'ALLINEC Vincent[1,13], MD, MSc; for the JENI Research Collaborative

1: Radiology Department, Angers University Hospital, Angers, France.
2: Neuroradiology-department, GHU-Paris, CH-Saint Anne, 1 rue Cabanis, 75014 Paris
3: Neuroradiology Department, CHRU de Tours, 2 bd Tonnelé, Tours, France Radiology
4: Department, University of Nantes Hospital, Nantes, France
5: Department of Diagnostic and Interventional Neuroradiology University Medical Center Hamburg-Eppendorf Hamburg, Germany
6: Department of Neuroradiology, Clinic for Radiology and Nuclear Medicine, University Hospital Basel, Basel, Switzerland
7: Department of Neuroradiology, Pitié-Salpêtrière Hospital, 75013, Paris, France
8: Department of Neuroradiology, University Hospital of Bordeaux, Bordeaux, France
9: Service de Radiologie, Hôpital Charles-Nicolle, CHU de Rouen, 37 boulevard Gambetta, Rouen, France
10: Department of Radiology, Dupuytren Hospital, Limoges University, France.
11: ENSC, Ecole Nationale Supérieure de Chimie | Laboratoire des Systèmes Électroniques, Traitement de l'Information, Mécanique et Énergétique. Ibn Tofail University, BP 133, 14000 Kénitra, Morocco
12: LTeN UMR-6607, Polytech'Nantes and RMeS UMRS-1229, University of Nantes, France
13: CNRS, INSERM, L'institut du thorax, University of Nantes, Nantes, Pays de la Loire, France.

ABSTRACT

BACKGROUND AND PURPOSE: Geometrical parameters including arterial bifurcation angle, tortuosity and arterial diameters have been associated in the pathophysiology of intracranial aneurysms (IAs) formation. The aim of this study was to investigate whether these parameters were present before or conversely resulted from the IA formation and growth.

METHODS: Patients from 9 academic centres were retrospectively identified if they presented a de-novo IA, or a significant IA growth on subsequent imaging. Geometrical parameters were compared between bifurcations with IA formation or growth as well as their contralateral side without IA and were extracted using a semi-automated algorithm. These parameters were compared in each patient at two different times using univariable, multivariable models and a sensitivity analysis with paired comparison.

RESULTS: 46 patients were included with 21 de novo IA (46%) and 25 significant IA growth (54%). The initial angle was not significantly different between IA-development group and the control one (129.7 ± 42.1 versus 119.8 ± 34.3; p = 0.264) but was significantly wider at the final stage (140.4 ± 40.9 versus 121.5 ± 34.1; p = 0.032), with a more important widening of the aneurysmal angle (10.8 ± 15.8 vs 1.78 ± 7.38; p = 0.001). The variations of the other parameters were not significant. These results were confirmed by the paired comparison.

CONCLUSION: Our study suggests that wider bifurcation angles, that have long been deemed causal factors for IA formation or growth, may rather be secondary to IA formation at pathologic bifurcation sites. This finding has implications on our understanding of IA formation pathophysiology.

Key Words: intracranial aneurysm – bifurcation – geometry – automated analysis algorithm

INTRODUCTION

The pathophysiology of IAs development is incompletely understood and many potential pathways are still active areas of investigation, including genetic, transcriptomic, and inflammatory imaging (1–3). IAs are preferentially located at proximal bifurcations of the circle of Willis, and several studies have provided insight into the geometrical characteristics of arterial bifurcations associated with IA formation and rupture (4–10). Indeed, the bifurcation angle has been shown to be larger on bifurcations harbouring IA, which constitutes a geometrical pattern that can influence flow and wall shear stress leading to higher risk of IA formation, growth and rupture (6–13).

However, a causal relationship has never been proved regarding the association observed between geometrical parameters and IA. In other words, one can argue that a remodelling of the bifurcation due to the IA itself can also account for the phenomenon observed (7).

In this multicentre retrospective study and through the comparison of geometrical parameters of bifurcations before and after IA formation or growth, we have investigated the chronology of this pathophysiological mechanism.

PATIENTS AND METHODS

Study design and participants

Analyses used data from a multicentre, retrospective, core lab adjudicated, cohort study of patients with de novo bifurcation IAs or bifurcation IAs that grew significantly during follow-up. This cohort results from the collaborative work of a trainee-led research network (Jeunes en Neuroradiologie Interventionnelle; JENI-RC (11)).

Patients were included from databases from nine University Hospital Centres (Angers, Basel, Bordeaux, Limoges, Nantes, Pitié-Salpétrière, Rouen, Sainte-Anne and Tours).

Local JENI-RC members were asked to provide de-identified data and images, for patients meeting the following criteria during longitudinal imaging follow-up: de novo IA development or significant growth of an IA over time, defined as an increase of at least 2,5 mm and at least 50% of the initial size during the follow-up.

Patients were excluded if they had a known connective tissue disorders (Marfan, Ehlers-Danlos, Autosomal dominant polycystic kidney disease, fibromuscular dysplasia, Moyamoya disease), a non-saccular IA, a non-bifurcation IA (including trifurcation or multiple-trunks IAs), or for which imaging exams were either unavailable or of insufficient quality for the analysis. Previously treated aneurysms with a neoaneurysm from the same neck were excluded.

For all patients, we collected two exams, with two similar imaging modalities where possible (MRI, CT-angiograms or 3D-DSA). The first one before the appearance or the growth of the IA, and a second one at the time of the IA discovery or when a significant increase of a known IA was diagnosed respectively.

Imaging studies of potentially eligible patients were transferred after complete anonymization to an expert neuroradiological core lab for post-processing.

This study was approved by the Institutional Review Board of Angers University Hospital (no 2020/130) and by the Commission Nationale de l'Informatique et des Libertés (ar20-0128v0).

Collected variables

Onsite investigators collected the following data, from electronic health records: baseline characteristics such as age, sex, cardiovascular risk factors (high blood pressure, smoking, alcohol consumption history), personal and familial medical history of IA (ruptured or unruptured), and treatment (statins, non-steroidal anti-inflammatory drugs and aspirin). The topography of the IA (posterior inferior cerebellar artery, basilar and posterior communicating artery aneurysms were considered as posterior aneurysms), the circumstances of diagnosis (ruptured or unruptured IA), the type of imaging (MRI, CT-angiograms or 3D-DSA) and the date at which each imaging were collected to define the follow-up intervals.

Bifurcation characteristics post-processing and measurements

To characterize the arterial bifurcations, we used a dedicated developed in-house vascular tree characterization software, reported in detail elsewhere (12). The accuracy of the results obtained has been tested beforehand and validated in dedicated studies (13).

The vascular compartment was isolated from all imaging studies with the use of a dedicated software (Slicer 3D, version 4.11.20210226 revision 29738 built 2021-03-01, Fedorov A. et al) (14). The cropped and segmented files were analysed by an algorithm developed by the RMeS laboratory and the Thorax Institute (UMR Inserm U1229, Université de Nantes, Oniris - Anass Nouri Ph.D, Florent Autrusseau Ph.D) in association with l'Unité de Recherche de l'Institut du Thorax UMR1087 UMR6291 (8 quai Moncousu - BP 70721 - 44007 Nantes Cedex 1 – France, Inserm).

In brief, the algorithm detects the centres of the different bifurcations by a graph-based approach and reproduces a three-dimensional skeleton of the vascular tree, the tracing of which is facilitated upstream by the segmentation. Various mathematical morphology tools are being exploited to obtain accurate measurements of the following anatomical properties: angles formed by the arteries at a given bifurcation, the diameters and cross-sections of each artery, and a measurement of arterial tortuosity.

Definitions of geometrical parameters

The initial ($\alpha_{initial}$) and final bifurcation angle (α_{final}) was defined as the angle between the daughter arteries, corresponding to the sum of the angles between the axis of the mother branch and the two daughter arteries on either side.

The minimal and maximal diameters of the vessel (Φ_{min}/Φ_{MAX}) are collected from two arteries' orthogonal plane (cross-sections) located at the very centre of the considered artery (2 planes are extracted 3 voxels apart from the centre).

Tortuosity (τ) of an artery can be defined by its degree of curvature. For each voxel of a target artery, the 3D normal vector is first computed. Then, its curvature degree is obtained by assessing the variations between its normal vector and the normal vectors of its neighbouring voxels. Once the curvature degree of each voxel is computed, the obtained values are averaged using a weighted-Minkowski sum in order to obtain a scalar between 0 and 1 reflecting the global tortuosity of the artery bifurcation. A scalar equal to 0 reflects a low tortuosity (straight artery) while a scalar near 1 reflects a high tortuosity. This method was validated through a comparison between its objective results and ground truth tortuosity measurements from human observers (13).

To determine if the geometrical changes during the follow-up were not only due to normal ageing of intracranial arteries, we extracted wherever possible the contralateral bifurcation to use the patients as their own control during the same timeline.

Statistical analysis

Statistical analysis was performed using JMP Pro 14 (SAS Institute Inc. 2015. JMP® Pro 14. Cary, NC: SAS Institute Inc) software. Continuous variables were summarized using means (± standard deviation, SD) or median (interquartile ranges, IQR) where appropriate, and discrete variables were summarized using counts (percentages).

Chi-square test, Fisher's exact test, t test, Mann-Whitney U test Wilcoxon signed-rank test were used as appropriate for the univariable analyses, with a p-value < 0.05 (two-tailed) as the threshold for statistical significance.

First, bifurcation features were compared between IA bifurcations and control bifurcations. Multivariable logistic regression model was used to determine factors that were independently associated with IA formation or growth. Hence, we examined putative risk factors for IA formation or growth, including all variables with a significant association in the univariate analyses (pre- defined $p < 0.1$). Furthermore, the initial bifurcation angle was examined, as debated clinical predictors for IA formation or growth in previous reports (7–10). Backward elimination was then used to remove non-significant variables ($p > 0.05$). The adjusted odds ratios (aOR) and 95% confidence interval (CI) of developing aneurysm were reported.

Sensitivity analysis with paired comparison was performed to assess for changes in the results when including only bifurcations with available control bifurcation using Wilcoxon signed-rank test (to consider the hypothesis where aneurysmal bifurcation and control bifurcation would be a matched sample).

Then, multiple linear regression model was used to determine the variables associated with the kinetics of the bifurcation angle change ($\Delta\ [(\alpha_{final} - \alpha_{initial})$/time of follow-up]). Likewise, we examined putative risk factors for this continuous endpoint, including all variables with a significant association in the univariate analyses (pre- defined $p < 0.1$) and backward elimination was used to remove non-significant variables ($p > 0.05$). The adjusted odds ratios (aOR) and 95% confidence interval (CI) were reported.

Finally, the relationship between the variation in bifurcation angle and in aneurysm size was tested by a linear regression analysis (with adjusted R-Square parameter).

RESULTS

A total of 66 patients were identified by onsite investigators and screened for inclusion. 20 patients were excluded: 11 were non-bifurcation IAs; 6 did not get a suitable exam before or after the birth or the growth of the IA, usually angiography exams without 3D-reformatable images; 2 had at least one of the two exams with a too low quality to be reliably analysed by the algorithm; 1 presented a non-significant growth of the IA during the follow-up after core lab assessment.

46 patients were included in the final statistical analysis including 21 with de novo IA (46%) and 25 with significant IA growth (54%). The follow-up ranged from 4 to 228 months, with an average follow-up of 84.8 months (7.07 ± 3.77 years).

Clinical and demographic characteristics are displayed in supplemental Table I. The overall mean age was 52.7 ± 15.3 years. There was a significant difference in age between the de novo IA group (44.8 ± 13.8) and the IA growth one (59.4 ± 13.4), but no difference for the other characteristics.

1. Aneurysm development and geometrical parameters of the arterial bifurcation

1.1. Stepwise logistic regression approach on the entire bifurcation cohort

Morphological features of the bifurcations are summarized in Table I. The initial bifurcation angle appeared to be wider in the aneurysmal bifurcation group, but this difference was not significant (129.7 ± 42.1 versus 119.8 ± 34.3; p = 0.264). The final bifurcation angle was significantly wider in the aneurysm bifurcations group (140.4 ± 40.9 versus 121.5 ± 34.1 p = 0.032), with an angle variation Δ ($\alpha_{final} - \alpha_{initial}$) of 10.76 ± 15.8 for the aneurysmal bifurcation angle versus 1.78 ± 7.38 for the control bifurcations (p = 0.001).

Two additional initial morphological parameters differed significantly between groups. The maximal diameter of the smallest daughter branch ($\Phi_{MAX\text{-}initial}$ DA_2) was bigger in the aneurysm group (2.44 ± 0.62 mm versus 2.15 ± 0.34 mm; p = 0.012) and the minimal diameter of the parent vessel

($\Phi_{min\ initial}$ PA) was smaller in the aneurysm group (2.33 ± 0.71 mm versus 2.61 ± 0.52 mm; p = 0.049). Both parameters were no longer significantly different at the final stage.

All the other initial and final morphological features did not differ significantly between groups.

After multivariable adjustment, only Δ angle ($\alpha_{final} - \alpha_{initial}$) remains significantly wider in the aneurysm bifurcation group versus control, aOR 1.08 [1.02-1.15] (p = 0.003). The initial bifurcation angle, the $\Phi_{MAX\text{-}initial}$ DA_2, and the $\Phi_{min\text{-}initial}$ PA, did not differ significantly between groups (all p > 0.05) (see supplemental data Table II for detailed aOR).

1.2. Sensitivity analysis and paired comparison of bifurcations with available control

In this analysis, a paired comparison of aneurysmal and contralateral bifurcations (n = 30 vs 30) was performed using the Wilcoxon signed-rank test. The variation (final measure – initial measure) of each morphological feature was tested (Table II). In this subset, morphological features which differed significantly between groups were: the Δ angle (5.8 ± 14.6 in the IA group versus 2.0 ± 9.3 in control; p = 0.002), the Δ Φ_{min} PA (2.33 ± 0.71 mm in the IA group versus 2.61 ± 0.52 mm in control; p = 0.022) and the variation of the maximal diameter of the largest daughter branch (Δ Φ_{MAX} DA_1) (-0.395 ± 0.95 in the IA group versus -0.11 ± 0.59 in control; p = 0.049). The variation of the other parameters did not differ significantly between groups.

2. Variables that influence the kinetic of bifurcation angle modification

In univariate analysis, the kinetic of angle change decreased significantly with increasing age (beta coefficient of -0.07 [-0.12 to -0.02]; p = 0.012 for each 10 years) and receiving statins treatment was also associated with a lower kinetic of angle change (0.04 ± 0.09 with versus 0.19 ± 0.3 without the treatment; p = 0.027). The other demographic and geometrical parameters did not significantly

influence the kinetic of bifurcation change. After adjustment in a multiple linear regression analysis, only higher age remained significantly associated with a lower kinetic of angle change (aOR 0.94 [0.89 to 1]; p = 0.046 for each 10 years).

3. Relationship between aneurysm size and bifurcation angle variations

In our sample, the relationship between the variation in aneurysm size and the variation in bifurcation angle was non-linear (R^2 = 0.01; p = 0.581; see supplemental Figure 1).

DISCUSSION

In this multicentre retrospective study and through the comparison of geometrical parameters of bifurcations before and after IA formation or growth, we found that IA development led to the enlargement of the bifurcation angle.

This finding challenges the classical thought that considers the bifurcation remodelling as responsible for aneurysm development.

Two previous works have analysed in vivo arteries with de novo IAs. The first included 3 patients of whom 2 probably had an unidentified systemic vascular pathology (15) and the second included 26 patients with 17 newly visualized aneurysms, but 6 aneurysms smaller than 2.0 mm (8). This latter study showed that the bifurcations with hypoplastic branches and with sharper angles between parent and daughter vessels were at higher risk of developing an aneurysm. However, the authors didn't analyse longitudinally the modification of the geometrical features precluding a formal comparison with our study.

Of note, the aging-related changes in the bifurcation angle, which in healthy individuals is of a small magnitude according to the baseline study by Żyłkowski et al. (2.0224 to 2.303° per decade) cannot account, alone, for our findings (16). Indeed, we provide a paired comparison analysis that shown a significantly more important variation on the pathological side when compared to the healthy contralateral angle in our sample, the latter showing a mean variation in angle close from the one expected according to Żyłkowski study.

We also found that older age was associated with lower longitudinal angle variations. This association could be explained by the stiffening of the arteries (17) that may have tended to attenuate the angle variation over time.

The widening of the bifurcation angle could be easily explained in the situation of a bulky IA which directly pushes the anatomical structures around by its mass effect, but this situation remains rare especially in our study where the mean aneurysmal diameter was around 6 mm and cannot explain how smaller aneurysms may have significantly affected the local geometry (see Figure 1).

Moreover, our results show a nonlinear relationship between the size of the aneurysm over time and the variation of the bifurcation angle, suggesting that it is not only the size of the aneurysm that influences the bifurcation geometry. To account for this finding, we hypothesize that, among possible other mechanisms, the IA may induce local inflammatory phenomena which remodel the artery wall and are responsible for the changes (18,19). Indeed, the flow distribution generates increased wall shear stress (WSS) in bifurcations leading when prolonged, on one hand to an intensified cell turnover in the vascular wall, and on the other hand, to decreased levels of endothelial nitric oxide synthase (eNOS) which normally reduces inflammation and stabilizes the wall structure by increasing the level of nitric oxide (NO) (20). Therefore, the aforementioned alterations may promote an inflammatory remodelling of the wall, which may in turn be responsible for the local geometrical parameters' modifications.

Contrary to previous works published, we found no difference in initial angle between the aneurysm-carrying – or doomed to be carrying – bifurcations, and the control bifurcations (6–10,21–27). Maybe due to our smaller sample size and different measurement tools, we were unable to replicate this finding. It should however be noted that in these latter studies, the measures deemed to predispose to the aneurysm formation were widely distributed around a predicted value, making it difficult to identify a true predisposing value.

Although these studies showed an association between bifurcation angles and the presence of aneurysm, like in middle cerebral artery (MCA) (8,9), no causal relationship can be conclusively determined as it is still possible that aneurysm formation is an epiphenomenon of larger bifurcations rather than a direct consequence of higher-risk bifurcation morphology as suggested by Baharoglu and colleagues (7).

The geometrical features we chose to focus on have already been linked to the flow parameters at bifurcation sites (21–23). Hence, modifications of these flow parameters are expected to change the local geometry, and vice versa a changing geometry should have an important impact on flow fields.

Several authors showed that the diameters of parental and daughter arteries are involved in aneurysm pathology as a contributing factor to aneurysm pathology (5,8–10).

In our study, we did not highlight any geometric differences at initial stage between groups, and neither any modifications of these parameters during the follow-up. However, due to the retrospective nature of the inclusions, we were unable to systematically provide the same imaging modalities during the follow-up, which constitutes a severe limitation to reliably compare the diameters of the arteries at initial and final stages, especially with time-of-flight studies that usually underestimate the calibres compared to contrast-enhanced vessels studies. It should be noted that this limitation was of no concern to tortuosity and angles which were only linked to the skeleton of the vascular tree.

Regarding the tortuosity, we also did not find any difference between the groups, nor any significant change in this parameter over time. Considering that this parameter evolves with ageing, we can assume that the mean follow-up time in our study was too short to unravel differences (16).

Beyond its novelty, the strength of our study includes the use of an automated algorithm for the parameters' assessments that reduces the variability of manual measurements. Here, we bring new insights and the basis for further studies evaluating the geometrical features' modifications of the circle of Willis on follow-up studies with automatized tools. Hence, depending on the geometrical modifications of a given bifurcation harbouring or not an IA, future studies can explore the probability of IA formation, growth, or rupture. More realistically, quantitative variables extracted from bifurcations would have to be included in composite scores along with clinical and biological parameters (28).

Due to the paucity of recorded events (de novo formation, or aneurysm growth), we acknowledge a relatively small sample size even if we were able to reach the statistical significance in part of our analysis. Furthermore, the retrospective design brings inherent selection bias as the exclusion of patients with poor imaging quality. Lastly, variability among machines that acquired the included imaging studies can also flaw, at least in part, the results of measurements.

CONCLUSION

Our study suggests that wider bifurcation angles, that have long been deemed causal factors for aneurysm development or growth, may actually be secondary to aneurysm development at pathologic bifurcation sites. This finding has implications on our understanding of aneurysmal development pathophysiology.

Collaborators : PASCO-PAPON Anne, GIROT Jean-Baptiste (University Hospital of Angers), MOUNAYER Charbel, SALEME Suzana (University Hospital of Limoges), BERGE Jérôme, BARREAU Xavier, MENEGON Patrice, TOURDIAS Thomas (University Hospital of Bordeaux), DETRAZ Lili, LENOBLE Cédric, ALEXANDRE Pierre-Louis, DAUMAS-DUPORT Benjamin (University Hospital of Nantes), CLARENÇON Frédéric, SOUROUR Nader-Antoine, LENCK Stéphanie, PREMAT Kevin (University Hospital of Pitié Salpétrière), PAPAGIANNAKI Chrysanthi, CURADO Adelya, LEFEBVRE Margaux, LE MOAL Julien, GERARDIN Emmanuel (University Hospital of Rouen), NAGGARA Olivier, TRYSTRAM Denis, BEN HASSEN Wagih (University Hospital of Saint-Anne), PSYCHOGIOS Marios (University Hospital of Basel), JANOT Kevin, PLANTY-BONJOUR Alexia (University Hospital of Tours)

Author contributions and acknowledgments:

- Boucherit Julien: collected data, performed the computational analysis and wrote the manuscript.
- Kerleroux Basile: collected data, performed the statistical analysis and critically reviewed the manuscript.
- Tessier Guillaume, Bourcier Romain, Rodriguez-Regent Christine, Sporns Peter, Ghannouchi Haroun, Shotar Eimad, Gariel Florent, Marnat Gaultier, Burel Julien, Ifergan Héloïse, Boulouis Grégoire, Forestier Geraud, Rouchaud Aymeric, Desal Hubert: collected data and critically reviewed the manuscript.
- Nouri Anass, Autrusseau Florent: developed the algorithm and critically reviewed the manuscript.
- Loirand Gervaise: critically reviewed the manuscript.
- L'Allinec Vincent: had the concept of the study, collected data wrote and critically reviewed the manuscript.

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FIGURES

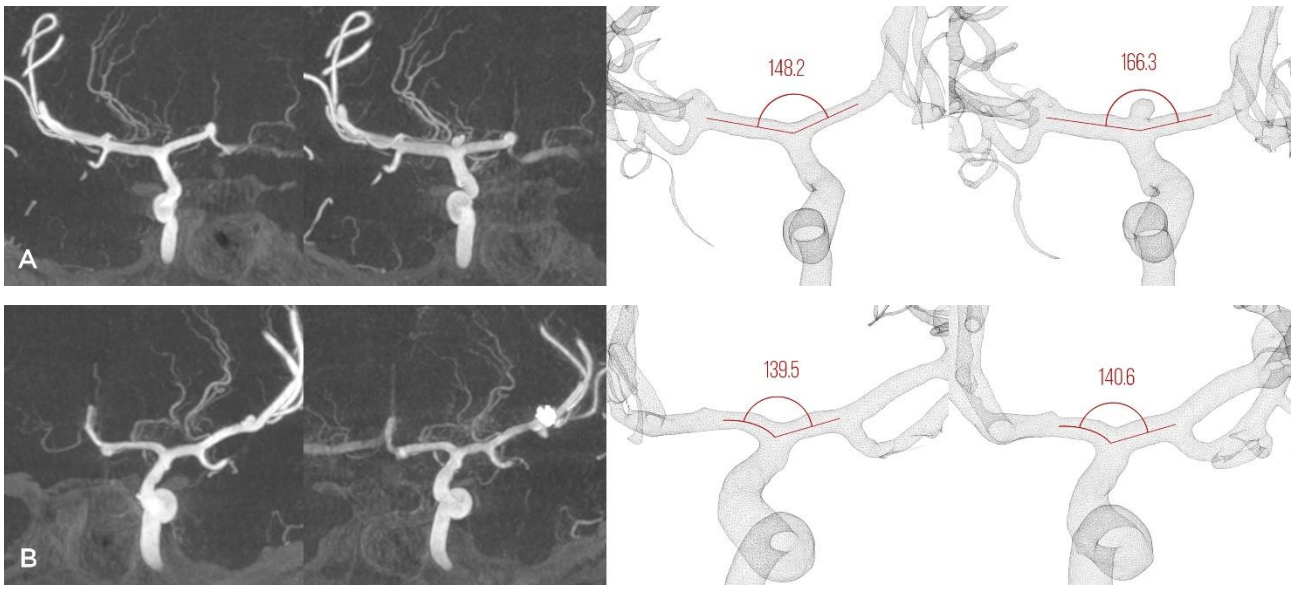

Figure 1. Angle modification over time

A. Widen angle with a small de novo unruptured intracranial aneurysm of the right carotid terminus – From 148.2° to 166.3°.

B. Contralateral bifurcation from the same patient – From 139.5° to 140.6°.

On both lines: Digital Subtraction Angiography with 10 mm Maximum Intensity Projection (left), and Volume Rendering (right). Interval time 96 months.

TABLEAUX

Table I. Bifurcations features: univariate analysis

	Aneurysmal bifurcations (n=46)	Control bifurcations (n=30)	p Value
INITIAL FEATURES			
Diameters (mm)			
$\Phi_{min\text{-}initial}$ PA	0.112 ± 0.71	2.61 ± 0.52	0.049
$\Phi_{MAX\text{-}initial}$ PA	3.22 ± 0.64	3.18 ± 0.49	0.742
$\Phi_{min\text{-}initial}$ DA_1	2.04 ± 0.61	2.22 ± 0.52	0.181
$\Phi_{MAX\text{-}initial}$ DA_1	2.88 ± 0.58	2.8 ± 0.49	0.533
$\Phi_{min\text{-}initial}$ DA_2	1.57 ± 0.49	1.64 ± 0.33	0.432
$\Phi_{MAX\text{-}initial}$ DA_2	2.44 ± 0.62	2.15 ± 0.34	0.012
Tortuosity $\tau_{initial}$ PA	0.88 ± 0.02	0.87 ± 0.03	0.504
Bifurcation angle α_{intial} (°)	129.7 ± 42.1	119.8 ± 34.3	0.264
FINAL FEATURES			
Diameters (mm)			
$\Phi_{min\text{-}final}$ PA	2.51 ± 0.64	2.43 ± 0.63	0.573
$\Phi_{MAX\text{-}final}$ PA	3.07 ± 0.53	3.07 ± 0.49	0.959
$\Phi_{min\text{-}final}$ DA_1	2.09 ± 0.76	2.17 ± 0.6	0.643
$\Phi_{MAX\text{-}final}$ DA_1	2.6 ± 0.65	2.65 ± 0.6	0.72
$\Phi_{min\text{-}final}$ DA_2	1.68 ± 0.46	1.65 ± 0.37	0.817
$\Phi_{MAX\text{-}final}$ DA_2	2.19 ± 0.48	2.08 ± 0.37	0.235
Tortuosity τ_{final} PA	0.88 ± 0.03	0.88 ± 0.03	0.545
Bifurcation angle α_{final} (°)	140.4 ± 40.9	121.5 ± 34.1	0.032
Δ Angle = α_{final} - $\alpha_{initial}$	10.76 ± 15.8	1.78 ± 7.38	0.001

Continuous values are expressed as means ± SD. Abbreviations: $\Phi_{min\text{-}initial/final}$ = initial/final minimal diameter; $\Phi_{MAX\text{-}initial/final}$ = initial/final maximal diameter; PA = parent artery; DA_1 = daughter artery, by convention the largest one; DA_2 = daughter artery, by convention the smallest one

Table II. Bifurcations features: Wilcoxon sign-rank test

	Aneurysmal bifurcations (n=30)	Control bifurcations (n=30)	p Value
Δ Diameters = Φ_{final} - $\Phi_{initial}$ (mm)			
Φ_{min} PA	0.11 ± 1.25	-0.03 ± 0.94	0.022
Φ_{MAX} PA	-0.41 ± 0.79	-0.16 ± 0.65	0.381
Φ_{min} DA_1	-0.04 ± 0.65	0.12 ± 0.99	0.859
Φ_{MAX} DA_1	-0.395 ± 0.95	-0.11 ± 0.59	0.049
Φ_{min} DA_2	0.06 ± 0.58	0.01 ± 0.34	0.684
Φ_{MAX} DA_2	-0.21 ± 0.61	-0.10 ± 0.49	0.233
Δ Tortuosity PA = τ_{final} - $\tau_{initial}$	0.002 ± 0.029	-0.002 ± 0.050	0.670
Δ Angle = α_{final} - $\alpha_{initial}$	5.8 ± 14.6	2.0 ± 9.3	0.002

Continuous values are expressed as median ± IQR. Abbreviations: $\Phi_{min\text{-}initial/final}$ = initial/final minimal diameter; $\Phi_{MAX\text{-}initial/final}$ = initial/final maximal diameter; PA = parent artery; DA_1 = daughter artery, by convention the largest one; DA_2 = daughter artery, by convention the smallest one

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Supplemental data – Table I. Demographic and clinical data of the study population

	De novo IA	Grown IA	Total	p Value
DEMOGRAPHY				
No. of patients	21 (46)	25 (54)	46 (100)	-
Sex ratio (H/F) †	0.4	0.47	0.44	0.807
Mean age in years ± SD*	44.8 ± 13.8	59.4 ± 13.4	52.7 ± 15.3	< 0.001
Cardio-vascular risk factors, no. (%)				-
Smoking history	14 (30)	13 (29)	27 (59)	-
Alcohol consumption history	2 (4.5)	3 (6.5)	5 (11)	-
High blood pressure	2 (4.5)	7 (15)	9 (19.5)	-
Long-term treatment, no.				-
Anti-inflammatory agent	0	1	1	-
Antiplatelet agent	5	5	10	-
Statins	1	4	5	-
IA history, no.				-
Personal of which ruptured	17 12	13 7	30 19	-
Familial of which ruptured	2 1	5 1	7 2	-
ANEURYSMAL CHARACTERISTICS				
Aneurysm location, no. (%)				-
Anterior circulation	16 (35)	18 (39)	34 (74)	-
Carotid terminus	5 (11)	1 (2)	6 (13)	-
ACA territory	3 (7)	5 (11)	8 (17)	-
MCA	8 (17)	12 (26)	20 (43)	-
Posterior circulation	5 (11)	7 (15)	12 (26)	-
Aneurysm size*				
Initial	-	3.72 ± 1.97	-	-
Final	5.91 ± 2.81	7.41 ± 3.74	6.73 ± 3.40	0.128
Rupture, no.	6	3	9	-

Continuous values are expressed as means ± SD. Abbreviations: ACA = anterior cerebral artery; MCA = middle cerebral artery

*Student's t-test; † Fisher's exact test

Supplemental data – Table II. Logistic regression for aneurysm development

	Odds ratio [IC 95%]	p Value
All patients (n=46 vs n=30)		
α_{final} - $\alpha_{initial}$	1.08 [1.02-1.15]	0.003
$\Phi_{min\text{-}initial}$ PA	0.72 [0.3-1.73]	0.462
$\Phi_{MAX\text{-}initial}$ DA_2	1.99 [0.64-6.16]	0.218
Initial bifurcation angle $\alpha_{initial}$ *	1.01 [0.99-1.02]	0.22

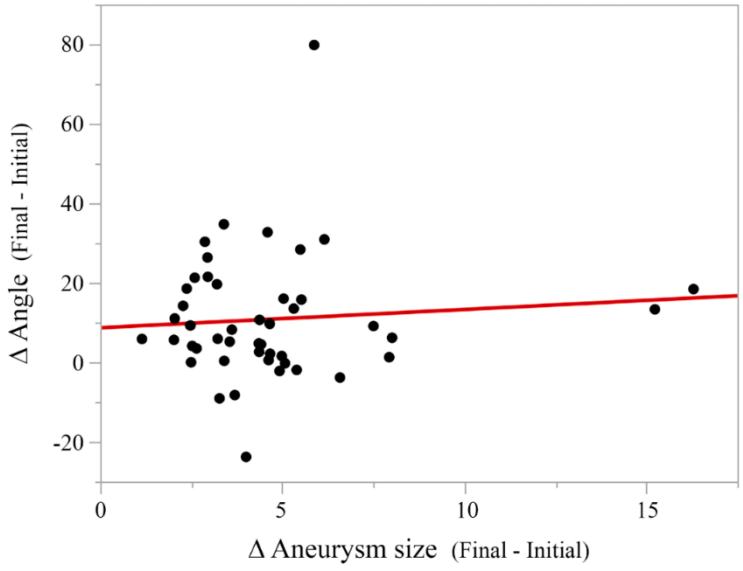
Variables tested were the significantly different ones on baseline features

*Variable not significant in univariate analysis forced into logistic regression

Supplemental data – Table III. Multiple Linear Regression for Δ Angle / Interval Follow up

	Odds ratio [IC 95%]	p Value
Communicant aneurysm	0.97 [0.88-1.07]	0.479
Hypolipemiant treatment (statins)	0.98 [0.85-1.13]	0.778
Personal history of aneurysm	1.06 [0.97-1.16]	0.196
Age (for each 10 years)	0.94 [0.89-1]	0.046

Supplemental data – Figure 1. Relationship between aneurysm size and bifurcation angle variations



The distribution of the dots suggests the absence of a linear relationship between the variation in aneurysm size and the one in bifurcation angle in our simple (R^2= 0.01; p = 0.581).

BOUCHERIT Julien

Modifications de la géométrie vasculaire des bifurcations intracrâniennes porteuses d'anévrysmes de novo ou en croissance. Etude multicentrique.

RÉSUMÉ

INTRODUCTION : Certains paramètres géométriques, notamment l'angle de bifurcation, la tortuosité et les diamètres des artères cérébrales, ont été associés à la formation d'anévrismes intracrâniens (AI). Le but de cette étude était de déterminer si ces paramètres étaient déjà présents ou au contraire résultaient de la formation et de la croissance de l'AI.

MATERIELS ET METHODES : Des patients de 9 centres hospitalo-universitaires ont été recrutés rétrospectivement dans cette étude s'ils présentaient un AI de novo, ou un AI ayant connu une croissance significative sur une imagerie de contrôle. Les paramètres géométriques mentionnés ont été extraits à l'aide d'un algorithme semi-automatisé puis comparés entre les bifurcations anévrysmales et leur côté controlatéral sans AI. Ces paramètres ont été comparés chez chaque patient à deux échéances différentes en utilisant des modèles uni et multivariés, et une analyse de sensibilité avec comparaison appariée.

RESULTATS : 46 patients ont été inclus avec 21 AI de novo (46 %) et 25 AI ayant subi une croissance significative (54 %). À la phase initiale, l'angle de bifurcation n'était significativement pas différent entre le groupe de bifurcations porteuses d'AI et le groupe témoin (129,7 ± 42,1 versus 119,8 ± 34,3 ; p = 0,264) mais devenait significativement plus large à la phase finale (140,4 ± 40,9 versus 121,5 ± 34,1 ; p = 0,032), avec un élargissement plus important de l'angle anévrismal (10,8 ± 15,8 vs 1,78 ± 7,38 ; p = 0.001). Les variations des autres paramètres n'étaient pas significatives. Ces résultats étaient confirmés par la comparaison appariée.

CONCLUSION : Notre étude suggère que des angles de bifurcation larges, qui ont longtemps été considérés comme des facteurs prédisposants à la formation ou à la croissance des AI, pourraient plutôt être secondaires à la formation d'AI sur certaines bifurcations pathologiques. Cette découverte a des implications sur notre compréhension de la physiopathologie de la formation de l'AI.

Mots-clés : anévrysme intracrânien – bifurcation – géométrie – algorithme d'analyse automatisée

Vessel's bifurcation geometry remodelling in de-novo and growing intracranial aneurysms. A multicentre study.

ABSTRACT

BACKGROUND AND PURPOSE: Geometrical parameters including arterial bifurcation angle, tortuosity and arterial diameters have been associated in the pathophysiology of intracranial aneurysms (IAs) formation. The aim of this study was to investigate whether these parameters were present before or conversely resulted from the IA formation and growth.

METHODS: Patients from 9 academic centres were retrospectively identified if they presented a de-novo IA, or a significant IA growth on subsequent imaging. Geometrical parameters were compared between bifurcations with IA formation or growth as well as their contralateral side without IA and were extracted using a semi-automated algorithm. These parameters were compared in each patient at two different times using univariable, multivariable models and a sensitivity analysis with paired comparison.

RESULTS: 46 patients were included with 21 de novo IA (46%) and 25 significant IA growth (54%). The initial angle was not significantly different between IA-development group and the control one (129.7 ± 42.1 versus 119.8 ± 34.3; p = 0.264) but was significantly wider at the final stage (140.4 ± 40.9 versus 121.5 ± 34.1; p = 0.032), with a more important widening of the aneurysmal angle (10.8 ± 15.8 vs 1.78 ± 7.38; p = 0.001). The variations of the other parameters were not significant. These results were confirmed by the paired comparison.

CONCLUSION: Our study suggests that wider bifurcation angles, that have long been deemed causal factors for IA formation or growth, may rather be secondary to IA formation at pathologic bifurcation sites. This finding has implications on our understanding of IA formation pathophysiology.

Keywords : intracranial aneurysm – bifurcation – geometry – automated analysis algorithm

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